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A Phase II Study of Delta-9-Tetrahydrocannabinol for Appetite Stimulation in Cancer-Associated Anorexia

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Abstract / Purpose: To evaluate the appetite-stimulating properties of delta-9-tetrahydrocannabinol (THC) in patients with anorexia due to advanced cancer. Patients and methods: Nineteen patients with various malignancies were entered. All had cancer-associated anorexia and a life expectancy greater than four weeks. Patients were started on THC 2.5 mg p.o. t.i.d. one hour after meals for four weeks. Evaluations for side effects, efficacy, acceptability and satisfaction were conducted at two and four weeks. Results: 18 patients were evaluable. Ten patients completed the entire 28-day study. Four patients experienced grade I toxicity and three withdrew at their request. Thirteen patients reported an improved appetite. Conclusion: THC is an effective appetite stimulant in patients with advanced cancer. It is well tolerated at low doses. Further studies are needed to determine the most appropriate dose and the specific population most likely to respond.

Résumé / Notre objectif consistait à évaluer les propriétés du delta-9-tétrahydrocannabinoïde (THC) chez les patients souffrant d'anorexie en raison d'un cancer avancé. Nous avons répertorié dix-neuf patients souffrant de diverses malignités. Tous soufraient d'anorexie associée à un cancer et leur espérance de vie ne dépassait pas quatre semaines. Les patients ont été traités avec le THC 2.5 mg p.o t.i.d., une heure après chaque repas et pour une durée de quatre semaines. On a procédé à des tests de contrôle après deux et quatre semaines, afin de déceler les effets secondaires, l'efficacité, la tolérance et le degré de satisfaction. Dix-huit patients ont ainsi été évalués. Dix patients ont complété l'étude d'une durée de 28 jours. Quatre patients ont souffer de toxicité et trois ont demandé leur retrait ; enfin, treize patients ont ressenti un regain d'appétit. En définitive, le THC stimule efficacement l'appétit chez les patients souffrant d'un cancer avancé et il est bien toléré à faibles doses. Des études subséquentes seront nécessaires afin de déterminer la dose la plus appropriée, et de cerner la population la plus susceptible de bénéficier de ce stimulant.

INTRODUCTION

Every year there are about 7 million new cancer cases and 5 million die worldwide (1). Anorexia and weight loss are common in advanced cancer. This is not a new problem; as early as 1932, Warren reported cachexia as the most common cause of death in cancer (2). In a prospective study of patients presenting to a palliative care program, 58% had lost greater than 10% body weight and 55% suffered from anorexia (3). There are few (4,5,6,7) effective treatments for this devastating problem. New agents to treat anorexia and weight loss in advanced cancer are needed.

The psychomimetic properties of various preparations of *Cannabis sativa* have been well known since antiquity. In the past 20 years, the scientific basis for its therapeutic potential has been developed. The active ingredient in cannabis, which is responsible for the observed activity, is delta-9-tetra-hydrocannabinol (THC) (8). Recently, its clinical use has been reported for many problems, such as raised intraocular pressure, seizures, and nausea and vomiting due to emetogenic cancer chemotherapy.

Many studies (Table 1) have now documented the antiemetic activity of THC (Dronabinol) when used to treat chemotherapy-induced nausea and vomiting. Appetite stimulation was reported in some of these investigations, but significant side effects were frequent at the doses used. We have conducted a phase II study of THC (Marinol, Roxane Laboratories) to stimulate appetite in anorexia due to advanced cancer.

PATIENTS AND METHODS

Patient Population

Between March 1990 and July 1991, advanced cancer patients presenting to the palliative care program of the Cleveland Clinic Foundation were screened for this trial. To be eligible, they had to have anorexia and a life expectancy of greater than four weeks. Patients were excluded if they were on

*A World Health Organization Demonstration Project

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Table 1 / PREVIOUS THC STUDIES

Reference	Patient Population	Dose	n =	Side effects	Appetite Assessed?
Sallan (16)	Cancer/Chemo Nausea/Vom		84	"High"	N
Regelson (15)	Cancer/Mood, Weight, Pain	0.1–0.34 mg/kg	54	Somnolence Dizziness	N
Chang (17)	Cancer/Young Nausea/Vom	10 mg/m² q3h	15	Somnolence Dizziness	N
Lucas (18)	Cancer Nausea/Vom	5 mg/m² q4h	53	Somnolence Psychosis	N
Frytak (19)	Cancer Nausea/Vom	15 mg t.i.d.	116	CNS	N
Sweet (11)	Cancer Nausea/Vom	5 mg/m² t.i.d.	25	Dizziness Somnolence	N
Underleider (13)	Cancer Nausea/Vom	7.5–12.5 mg q4h	214	Somnolence Dizziness	Y*
Lane (12)	Cancer/Nausea/ Vomiting	10 mg q6h	60	Neuropsychotropic	N
Ekert (14)	Cancer/Nausea/ Vom/Children		19	Drowsiness	Y*

* Appetite was assessed only on the day chemotherapy was given.

Table 2 / PATIENT CHARACTERISTICS

No.	Initials	Gender	Age	Diagnosis	Dose/m²
1	PC	M	65	Esophagus	1.47
2	RB	M	71	Bladder	1.69
3	SM	M	81	Prostate	1.15
4	CY	F	62	Breast	-
5	RF	F	62	Unknown Primary	1.92
6	PP	M	52	CML	1.34
7	WW	M	59	Pancreas	1.34
8	FF	F	66	Pancreas	2.12
9	TT	M	62	Pancreas	-
10	HB	M	74	Prostate	1.47
11	VS	M	67	Bladder	-
12	GH	M	75	Pancreas	1.64
13	HB	M	60	Renal	-
14	MG	F	63	Lung	2.05
15	FP	M	54	Unknown Primary	-
16	DT	F	61	Carcinoid	1.60
17	RD	F	71	Lung	1.67
18	AK	M	62	Mesothelioma	1.28
19	WL	M	70	Prostate	1.36

other drugs known to affect appetite, had a history of allergy or adverse reaction to THC or other cannabinoids, a history of significant arrhythmias or cardiac disease (New York Heart Classification III or IV), were currently receiving chemotherapy and/or radiotherapy or hormonal therapy if the dose was not stable during the preceding two weeks or would not remain stable throughout the entire study, were receiving enteral or parenteral feedings, had malabsorption or mechanical obstruction, or had a history of anorexia nervosa, illicit drug abuse, major psychiatric disorder, or inadequate renal/hepatic function. After eligibility was determined, all patients gave written, informed consent which had been approved by our institutional review board. Nineteen patients (Table 2) with various malignancies were entered.

Study Design

Each patient entered had a complete history and physical exam, including weight, height, anthropometric measurements, and Folstein's mini-mental status exam. Patients were not weighed if they had third space fluid accumulation, were confined to bed, or were unable to return to the clinic at the completion of the study. Before beginning treatment, a side effect profile (Table 3) was completed. Patients were then started on THC 2.5 mg p.o. t.i.d. one hour after meals. Patients over the age of 65 were given 2.5 mg b.i.d. for three days and then increased to the regular

Table 3 / SIDE EFFECTS PROFILE

Anxiety
Depression
Dizziness
Drowsiness
"High"
Inability to Concentrate
No Energy
Palpitations

dose if well tolerated. Each week, one 24-hour food diary was recorded by the patient. At the end of two and four weeks, patients returned for a follow-up visit. At that time, a physical exam, mini-mental status exam, and the side effect profile was repeated.

At the four-week visit (or the end of study), patients were asked the following three questions: (a) Since starting this drug, has your appetite shown no improvement, shown slight improvement, shown major improvement, or become completely normal? (b) Are you satisfied with the way this drug affected your appetite: unsatisfied, slightly unsatisfied, satisfied, or very satisfied? (c) Would you like to continue taking this drug in the future: would choose a different drug, it doesn't matter which drug, would probably choose this drug, or would much rather have this drug?

In addition, weight and anthropometric measurements were obtained where possible. Patients were considered to respond to treatment if they answered "slight improvement" or better on the first question. Satisfaction and acceptability were evaluated by the second and third questions, respectively.

Patients were considered evaluable for toxicity after one dose of THC and for efficacy after three doses. Patients were removed from the study for grade III/IV toxicity. If toxicity was minimal, patients were given the option to withdraw from the study or have the dose stopped, or reduced temporarily and restarted at the previous or lower dose when side effects subsided. If patients had a positive response to the drug without adverse reactions, then at the completion of the study they were given the option to continue at the present or higher dose (2.5–5.0 mg b.i.d.–t.i.d.) in an open study.

RESULTS

Nineteen patients were entered (Table 4) and 18 were evaluable for efficacy and side effects. Patient #4 withdrew consent after two doses. Twelve men and six women were evaluated. The median age was 64 years (range, 52–81 years). Ten patients completed the full 28 days. Of the eight who did not, the median time on study was three days (range, 3–21 days). Three participants (#3,7,11) withdrew due to grade I side effects, three (#9,15,18) did not complete 28 days due to decreasing performance status, one (#14) began radiation treatment, and one (#17) simply refused to answer questions after 21 days.

Overall, 13 of 18 had improved appetite as judged by their response to question 1. Ten responded with "slight improvement" and three had a "major improvement". We were unable to correlate this re-

Table 4 / RESULTS

No.	Initials	Days[1]	S/E[2]	PS[3]	Weight[4]	CC[5]	Res[6]	Sat[7]
1	PC	28	N	1	NC	+	Y	Y
2	RB	28	N	1	NC	+	Y	N
3	SM	14	Y	2	+	+	Y	Y
4	CY	<1	N	1	-	-	-	-
5	RF	28	N	1	DECR	+	Y	Y
6	PP	28	N	0	+	+	Y	Y
7	WW	2	Y	2	-	-	N	N
8	FF	28	Y	1	-	NC	Y	Y
9	TT	3	N	3	-	-	N	-
10	HB	28	N	2	-	-	Y	Y
11	VS	2	Y	1	-	-	N	N
12	GH	28	N	2	-	-	Y	N
13	HB	28	N	3	-	-	Y	N
14	MG	12	N	1	-	-	Y	Y
15	FP	3	N	3	-	-	N	-
16	DT	28	N	2	-	+	N	N
17	RD	21	N	3	-	+	Y	N
18	AK	4	N	2	-	-	Y	-
19	WL	28	N	1	+	+	Y	Y

[1] Total number of days on study
[2] Side effects
[3] Baseline Performance Status
[4] Change in Weight: +=increased, DECR=decreased, NC=No Change, -=Not Weighed
[5] Change in calorie count
[6] Response to treatment: Yes/No
[7] Satisfied with the drug: Yes/No

sponse with the dose/metre² ratio (r=0.16, Spearman's rank correlation). Nine of the 10 who completed the full 28 days were responders.

The median baseline performance status (Eastern Cooperative Oncology Group) was 2 (range, 0–3). The median completion score was 1 (range, 0–3). The median baseline mini-mental status exam score (total possible = 30) was 29 (range, 13–30). The median completion score was also 29 (range, 20–30). Five patients (#1,9,11,14,20) had a drop in their score from baseline to completion. The median change was 2 (range, 1–3). All were responders and three choose to continue the drug in the open study.

Six patients had both pre-study and end-of-study weights recorded. All six were responders; five completed the 28 days. Three patients gained weight (#3,6,20), two maintained a stable weight (#1,2) and one patient (#5) lost weight. The median gain was 1.3 kg with a range of 1.0–2.7 kg. Patient #5 lost 6.7 kg.

Calorie counts were available for nine patients; seven (#1,2,5,6,8,16,19) of these completed all 28 days, #17 completed 21 days and #3 completed 14 days. Eight (#1,2,3,5,6,16,17,19) of the nine patients increased their calorie count from baseline. One patient (#8) had a stable calorie count. The median increase in calorie count was 1,032 kilocalories/day (range, 574–2,436) or 4,334 kJ/d (range, 2,411–10,231).

Four patients experienced side effects. Patient #3 had grade I slurred speech and withdrew after 14 days, #7 and #11 had grade I nausea and both withdrew after two days, #8 had grade I nausea but completed the 28-day study after a temporary decrease in dose. Patients #3 and 8 were responders, #7 and 11 were not. All three patients withdrawn from the study due to side effects were men. The median age of patients with side effects was 67 years (range, 59–81); of those without side effects was 63 years (range, 52–75; p=0.5, Mann-Whitney). The median dose/metre² was 1.34 mg in those with side effects versus 1.53 mg in those without side effects (p=0.5, Mann-Whitney).

DISCUSSION

Five previous studies have attempted to evaluate the appetite-stimulating effect of THC. Two of these (9,10) were conducted in healthy, young volunteers. Both studies demonstrated increased appetite with treatment. Although these results support the need for further investigation, they cannot necessarily be extrapolated to a population with anorexia due to advanced cancer. Two studies (11,12) evaluated food intake, but that was not their primary objective. Underleider et al. (13) and Ekert et al. (14) used THC for chemotherapy-induced nausea and vomiting. Both studies recorded food intake, but only on the day of chemotherapy treatment, demonstrating that alleviating nausea and vomiting does, coincidentally, increase food intake. However, in our population, none of the participants reported these symptoms in the initial screening phase, suggesting that this was not the mechanism of appetite stimulation in our patients.

Regelson et al. (15) evaluated the antidepressant and appetite-stimulating properties of THC in cancer patients. There were problems with the study design. It is not specified if patients suffered from anorexia and appetite was not evaluated, although that was a defined objective. Weight gain was the parameter used to indirectly evaluate appetite. This may be misleading, since in advanced cancer appetite may be stimulated to the satisfaction of the patient but weight gain may not follow.

Unlike our patients, Regelson's participants experienced significant side effects. In the initial study, seven of 10 patients experienced somnolence and dizziness. We had none. The dose used in Regelson's study was 0.1–0.34 mg/kg q.i.d.. That is roughly 10 times the dose we used. In the second phase of their study, 18 of 58 patients had side effects, most commonly dizziness and somnolence again. The dose in the second phase was lowered to 0.1 mg/kg t.i.d.; this was still significantly greater than ours.

The high doses are most likely the reason for the side effects, which were not seen in our population. The timing of their dose was also different. Anticipating side effects, we administered the drug one hour after meals to slow absorption and decrease the "bolus" effect. In contrast, Regelson's group ingested the medication one hour before meals.

In our study, appetite was evaluated by questioning the patients. Thirteen of 18 demonstrated a positive response to the appetite-stimulating effects of 2.5 mg THC one hour after meals. Although our results do not suggest a dose response, our clinical impression supports this possibility. It appeared that the two very small women (#8 and #14) in the study enjoyed good responses. Both patients reported that they were hyperphagic. Further support for a positive dose-response relationship was another anecdotal report from patient #5. Before the study she had been given THC 10 mg t.i.d.; significant appetite stimulation was noted but confusion occurred and the drug was stopped. One month later she was enrolled in the study. Upon completion (without side effects), she noted that she was much more satisfied with the way the higher dose had affected her appetite.

Although six of our patients had worsening performance status, as might be expected in this popu-

lation, only three withdrew from the study before 28 days. Neuropsychological side effects have been the most serious problems with THC in previous studies. This may be due to the higher doses, as our patients maintained their mini-mental status exam scores overall. Of the five patients whose scores decreased, all completed 28 days and all were responders.

Only one of the 13 who were weighed lost weight during the study and seven of the nine who kept diaries increased their calorie count; however, the significance of these results cannot be determined since data were not available for all patients.

Only four patients reported side effects. It is interesting that only one effect could be considered neuropsychological (slurred speech). This is in contrast to previous studies in which such effects predominated. In particular, none of our patients had problems with somnolence.

Since THC has been used to treat chemotherapy-induced nausea/vomiting, we were surprised to find nausea the most common side effect. This most likely represents a previously unidentified side effect, as it was also seen on eight occasions in Sweet's (11) study. Although three out of four of the patients with side effects withdrew from the study, this may not have been necessary, as all experienced grade I toxicity and a temporary dose reduction may have allowed continued treatment. This was clearly the case with patient #9. It is fortunate that a "high" was not necessary to obtain appetite stimulation, as it was in many antiemetic studies (16).

From this open, non-masked study, we conclude that THC is a potentially useful drug to stimulate appetite in advanced cancer. At low doses, administered one hour after meals, it is well tolerated. Toxicity is infrequent, mild, and reversible with dose reduction. Further controlled studies are needed to further determine the efficacy, appropriate dose, and patient population most likely to benefit.

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